Integrated network pharmacology and zebrafish model to investigate effects components of Origanum valgare for treating Alzheimers Disease

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Abstract

Origanum vulgare ssp. hirtum is a medicinal herb that promotes antioxidants, anti-inflammatory, antibacterial, and its neuroprotective effects. Here the research investigates the preventative impacts and the procedure of O. vulgare ssp. hirtum essential oil (OEO) on the impairment of cognitive and brain oxidative stress in a scopolaminedecreased uneasy-like behaviour and enhanced mental capacity. Our findings show that exposure to Sco (100 M) causes problems with anxiety, spatial memory, and novelty response. The OEO injection also lessened the impact of Sco on antioxidant stress and acetylcholinesterase (AChE).

The OEO mix was perceived by the gas chromatography-mass being thymol (27.83%), p-cymene (19.22%), and -terpinene (20.59%). These results point to OEO's potential to reverse the cognitive deficiencies caused by Sco by reactivating the cholinergic procedure and boosting brains antioxidant levels. OEO could therefore be employed as a possible source of bioactive chemicals that exhibit beneficial biological actions and have the potential for medicinal usage.

Keywords: Zebrafish model, Guiera senegalensis**,** Alzheimers Disease, Origanum valgare

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Overview

Aromatherapy is the supervise application of herbal essential oils that have been condensed, flowers, and other plant materials for therapeutic or preventative purposes. The three primary routes by which essential oils are delivered are orally, topically (aromatherapy massage), and olfactorily (direct and indirect inhalation). Essential oils' antifungal, antiviral, antibacterial, and antioxidant properties are their main pharmacological advantages.

Numerous authors have recently emphasised the advantages of aromatherapy for reducing stress, restoring mental well-being, and relieving anxiety and despair.

Origanum majorana L. (Lamiaceae), also known as marjoram, is a herb that is native to the Mediterranean region and is grown in many countries in, North Africa,Europe and Asia.

Popular spice marjoram has a powerful & alluring scent. Asthma, dyspepsia, headaches, and rheumatism are just a few of the diseases for which this herb has been used in folk medicine. Numerous authors have discussed marjoram's impact on various illnesses as well as its antibacterial, antiviral, antioxidant, anti-acetylcholinesterase (AChE), anti-metastatic, and anti-tumor growth properties. Recent research has revealed that Origanum majorana essential oil (OmEO) can mimic the effects of antidepressants by modulating the noradrenergic, dopaminergic, and serotonergic systems. Another group of researchers discovered that OmEO helped bruxism patients feel less anxious, and they hypothesised that this essential oil would be a safe alternative to benzodiazepines in the treatment of bruxism. O. majorana also possesses anti-inflammatory properties. [21].

The structural and functional similarity between the blood-brain & barrier (BBB) of the zebrafish and mammals, as well as the existence of many proteins that are related to human assisted neurodegenerative diseases in the zebrafish, highlight the possibility of molecular cellular features that are easily observable being conserved. Other significant benefits of this animal model are also present.

Zebrafish embryos serve as evidence that mobility is a complex habit, as they continue to posses a foundational capability to swim long after the hatching. The neocortex is deficient in the zebrafish, yet the synapse structures are as yet unblemished and are believed to be engaged with the transmission cycle as well as learning and memory. Even if there is a significant association between the various brain regions' functioning in zebrafish, this is nonetheless the case.

It is generally known that cholinergic signaling contributes to both memory and learning consolidation. Scopolamine (Sco), a nonselective muscarinic acetylcholine receptor antagonist, reduces learning and short-time memory and causes amnesia. In the object identification test, Sco reduces the ability of rodents to establish memories and weakens their cognitive abilities. Zebrafish, who are likewise entirely powerless against Sco, show amnesic impacts in the clever item acknowledgment (NOR) and Y-labyrinth tests. Sco-instigated amnesia models are thusly ordinarily used to assess the potential for neuroprotection of related substances and regular items.

The bulk of the Origanum species are indigenous to the Mediterranean, North Africa and Eurasia and are used in classical medications to cure gastrointestinal, respiratory, and cold-related conditions. The Origanum genus is a part of the Lamiaceae family. O. syriacum L. has been demonstrated to have neuroprotective properties and to be advantageous in the treatment of a range of ailments that impact numerous body systems, including the respiratory, cardiovascular, and neurological systems. Additionally, it improves memory and learning in mouse models of AD. The antioxidant, antibacterial, and anti-inflammatory capabilities of origanum's phenolic parts were traditionally thought to be responsible for the therapeutic actions of the herb in conventional medicine. O. vulgare's anti-inflammatory features have been investigated in numerous studies utilizing two of them cell and animal-based modelling. Avola et al. represented the anti-inflammatory and wound-healing properties of O. vulgare L. essential oil in a person keratinocyte cell culture. Han and Parker have provided affirmation of the anti-inflammatory, tissues re-modelling. Studies into the antioxidant benefits of O. vulgare, especially those of its essential oil derivatives, have been extensive. The chemical combination of O. vulgare essential oil contains carvacrol (35.00%) and thymol (35.19%), which is primarily to blame for Kakhri's demonstration of the oil's highest antioxidant activity.

Materials and Methods

Using and Extracting Plant Material

In the Touloum area, fresh Guiera senegalensis leaves were picked in June 2021. (Far North,Cameroon). The plant was identified

botanically by comparison to a botanically sample of Sabatié B. No. 698, which was discovered and got registered under No. 49838/HNC, at the National Herbarium of Cameroon.

The extraction process was followed exactly as Imam et al. [40] had previously reported.

Fresh G. senegalensis leaves were reduced to a fine powder after being dried in the shade for 1 week. The powder in result, 300 g, was macerated for 74 hours in a solvent made up of 80% ethanol and 25% distilled water. Whatman paper was used to filter the mixture. The final product was evaporated at 80°C in a rotating vapor to eliminate the ethanol and at 50°C for 45hours in an oven to remove the water. 7.67% (v/v) of the hydroethanolic extraction yield was obtained.

High-Performance Liquid Chromatograph (HPLC-PDA)

The extracts was initially diluted in a 3:7 methanol to H2O solution to create a stock solution with an initial concentration of 5 mg/mL. Clarifying the solutions required the use of a 0.2 m Millipore filter

The quaternary pump produced the mobile phase throughout the analysis by combining The sample analysis was done at a rate of flow 0.9 mL/min. Utilizing aliquots, the diluted extract was delivered in linearity gradients. For alignment bends with connection coefficients more noteworthy than 0, standard stock . Identification was done by comparing UV spectra and retention times, taking into account a match index of at least 950/1000. Sigma Aldrich provided all of the HPLC solvents and quality standards (Darmstadt, Germany).

Treatment and Animal

Adult fish received commercial flake fish feed twice daily (Gadstrup, Norwin Noryitall, Norwin, Denmark). Prior to the start of the study, fish was acclimated for 1 week.

Before the commencement of the behavioural tests, a 500 mL glass containing GS (1, 4, and 8 g/L) and Sco (100 M) was immersed once daily for an hour All strategies and conventions including the consideration and utilization of lab creatures have been supported by the Workforce of Science's Creature Exploration Morals Board of trustees at Alexandru Ioan Cuza College of Iaşi, Romania (No. 15308/30.07.2019), which found that they completely conformed to Order 2010/64/EU of the European Parliament and Gathering of September 22, 2010 on the insurance of creatures. The utilization of creatures was diminished to a base, and endeavors to improve

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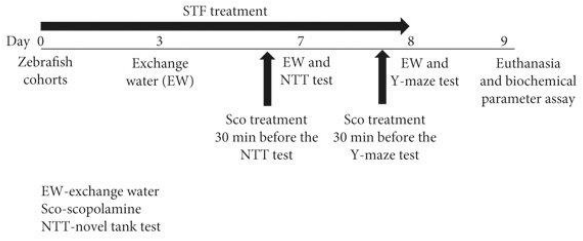


Figure 1: Design Procedure of experiment

Novel Tank Diving Test (NTT)

According to Cachat, the NTT is a specialized test utilized to measure zebrafish locomotor activity and anxiety reaction. The NTT was a 1.4 L trapezoidal tank (14.1 x 25.8 x 5.1 cm) with top and bottom parts separated by a virtually horizontal line. Zebrafish were evaluated one at a time for 6 minutes. Distance walked and average speed were the locomotor activity endpoints (measured in m and m/s, respectively). The quantity of passages to the top, time spent at the top (s), normal passage length (s), absolute distance went in the top (m), and freeze term (s) endpoints were evaluated to recognize tension like way of behaving.

Y-Maze Test

To find out how the zebrafish would react in an unknown setting, the Y-maze test was utilised. Zebrafish were put in the novel arm of a Y-shaped glass tank to test their recall (27 8 15 cm for each arm, 4 L). The "start" arm, "other" arm (which was consistently open), and "new" arm were the names of the Y-labyrinth arms (obstructed in instructional meeting and opened in test meeting). The fish were each independently positioned in the start arm, and the new arm was shut, for the term of the preparation (5 minutes). The fish were set in the beginning arm once more, yet this time the new arm was opened, and testing for five minutes began following an hour. Outright distance traveled (m) and turn point () were used to evaluate locomotor activity, while time spent in

the sharp arm (% of hard and fast arm time) was utilized to survey the reaction to interest.

Novel Object Detection Test

The NOR, a behavioral experiment, is often used to study the memory function of zebrafish. Zebrafish were introduced to the novel tank for a total of 5 minutes over the course of 3 days without the objects (30 cm filled with 6 cm of water). Zebrafish were exposed for ten minutes on the fourth day to two similar objects (training phase).

Results and Discussion

Extract from Guiera senegalensis: Chemical Makeup

The study was done to determine the chemical composition of the GS extract. According to the findings, several flavonoids and polyphenolic acids were identified. The following quantities were discovered: rutoside (204.81 g/g of dry extract), quercetin (305.6 g/g of dry extract), quercetin3-O-arabinoside (312.40 g/g of dry extracts), catechin (108.54 g/g of dry extracts), and luteolin-7-Oglucoside (55.35 g/g of dry extracts).

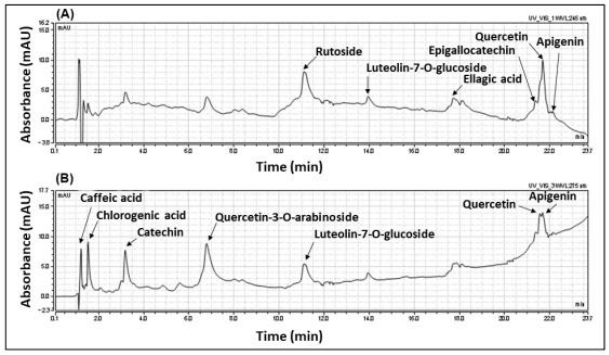
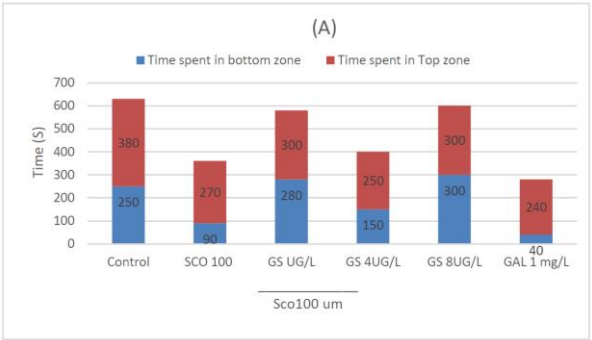


Figure 2: LC-PAD chromatography profile

Various distributions have exhibited that the vegetal material from G. senegalensis utilized in traditional medication contains in excess of 46 mixtures. According to earlier published data, chemicals that are similar to those in our results have been discovered in the leaves of G. senegalensis. In any case, most of the ongoing information just gives a conventional distinguishing proof without the measurements of these mixtures. Extractability is connected with the plant material, the solvent, and the preparation process. The most common combinations described included different polyphenolic acids, flavonoids, and gallic acid derivatives. As per the synthetic arrangement, the examined remove gives off an impression of being rich in polyphenols (flavonoids, catechins, and polyphenolic acids), which are referred to work as normal cell reinforcements. The free hydroxyl moieties likewise enact a safeguard component against free radicals in addition to connecting with cell layers. Additionally, quercetin, apigenin, and catechin derivatives inhibit oxidative enzymes like lipoxygenases to stop the denaturation of cells.

Impact of the NOR, Y-Maze and NTT Tests on Zebrafish Anxious Behavior and Spatial Memory

Zebrafish are in many cases utilized in the new tank plunging test (NTT) to analyze the impacts of uneasiness. The GS treatment brought about huge changes in the top/base proportion, complete distance went in the top zone, number of sections to the top, and time spent in the highest point of the tank, as per the one-way of ANOVA. Following Sco treatment, there was a sensational decline (p 0.0001) in how much time spent in the top zone of the tank, the top/base proportion, the distance went in the top zone, and the quantity of doorways to the top contrasted with the benchmark group (p 0.0001). Furthermore, the Sco-organization diminished the locomotory design in contrast with the benchmark group. For contrast, GS treatment had anxiolytic-like effects in Sco zebrafish at all dosages (1 g/L, 4 g/L, and 8 g/L). Iripramine (IMP), a favourable reference drug, showed anxiolytic effects.



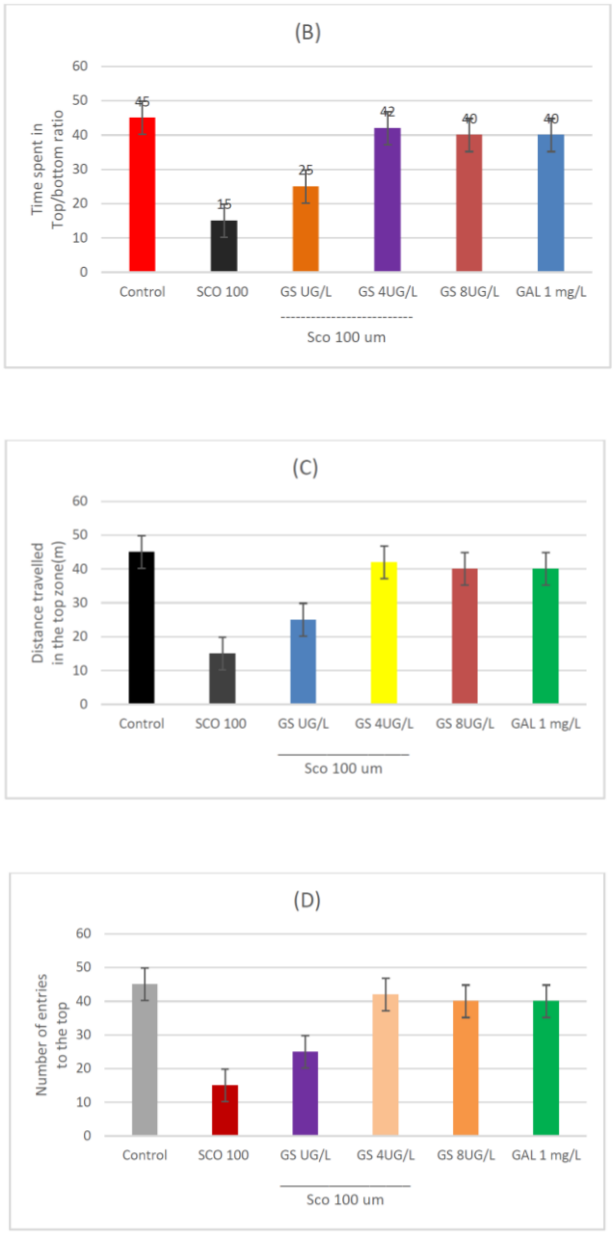


Figure 3: Guiera senegalensis hydroethanolic extract

Our findings confirm past research suggesting GS may have a neuroprotective effect. Sombie suggests a new possible source of naturally occurring neuroprotective and antioxidant components: the galls from G. senegalensis.

Additionally, Somewhat's exploration uncovered that G. senegalensis is as a treatment mental and neuropsychiatric sicknesses in the Hauts-Bassins locale of Burkina Faso. As per the creators, the advantages were achieved by the presence of the neuroprotective mixtures.

These results suggest that GS may be considered a therapeutic medication with a high potential for enhancing cognitive impairments. In fact, we demonstrated that GS has cognitive-improving and anxiolytic properties using the Sco zebrafish model.

Impact on AChE Activity in the Brain

AChE activity was investigated to learn more about the GS mechanism in the Sco zebrafish model. In mild cognitive impairment, AChE activity represented cholinergic status. When processing memories, the cholinergic system is crucial, and cholinergic neurons are destroyed. Acetylcholine levels fall as a result of AChE, which causes the learning and memory impairments associated with AD. Additionally, AChE inhibitors are implied in AD therapy, which improves cholinergic neurotransmission.

The AChE activity in the zebrafish treated with Sco was extremely higher than in the control group (p 0.0002). Additionally, the GS treatment significantly decreased the Sco-mediated AChE aggravation at all dosages (p 0.0001). The GS has cholinesterase inhibitory potential, which is connected to zebrafish with superior memory capacity, according to the results of the NTT, Y-maze, and NOR tests. Inhibiting AChE can be used to treat dementia caused by Alzheimer's disease, Parkinson's disease, senile dementia.

Particularly at low doses, GS dramatically reduced the In the zebrafish brain, Sco causes a rise in AChE. Since it modifies mental capability, hippocampal Hurt is a significant supporter of dementia-related cognitive declines and the fundamental component of mental problems..

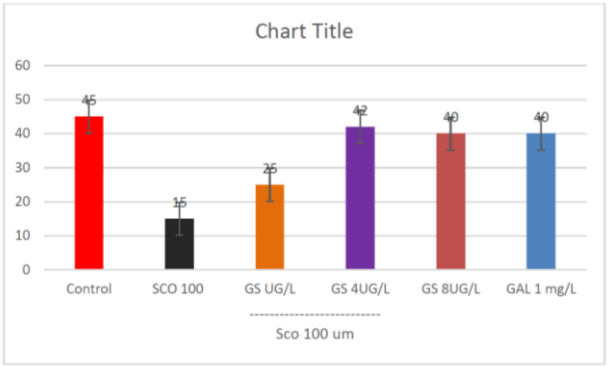


Figure 4: Impact of Guiera senegalensis hydroethanolic extract

Brain antioxidant capacity effects

The oxidative stress indicators were assessed to see if GS boosts antioxidant capability in vivo. Following exposure to Sco, Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), total reduced glutathione (GSH), as well as protein carbonyl (p 0.0001) and lipid peroxidation (malondialdehyde—MDA) activities, all extremely decreased (p 0.0003).

Additionally, GS treatment (1 g/L, 4 g/L, and 8 g/L) significantly reversed the fall in CAT,SOD specific activity, GPX, and the overall amount of reduced GSH (p 0.001, 0.0001, and 0.0004, respectively) (p 0.0001). In addition, animals treated with Sco had extremely lower levels of protein carbonyl (p 0.0001) and MDA (p 0.001) after receiving GS therapy, which in turn decreased protein and lipid peroxidation.

Conclusions

In this work, the chemical composition of OmEO was first determined, then the proteomes of AD model rats were analysed to look for any molecular alterations. This approach indicated four biological processes as potential OmEO side effects that might affect rat brain (hippocampi) performance: apoptosis, oxidative stress, neuriinflammation and cognitive processes mediated by neurotrophins.

Testing corresponding targets—recognized representatives of the biological processes of interest—led to the determination of the relevance of the biological processes in question. In this work, we discovered that OmEO improved cognition in rats treated with A1-42 and decreased brain oxidative stress. In order to demonstrate that OmEO improves memory performance in rats given A1-42 treatment, we finally connected the cellular and molecular findings with behavioural data.

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